PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

ISHIDA, Takashi
A. Aoki, Ishida & Associates
Toranomon 37 Mori Building
5-1, Toranomon 3-chome
Minato-ku
Tokyo 105-8423
JAPON

43

Date of mailing (day/month/year)	
18 April 2000 (18.04.00)	
Applicant's or agent's file reference G899-PCT	**IMPORTANT INFORMATION**

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/JP99/04503	20 August 1999 (20.08.99)	21 August 1998 (21.08.98)

Applicant
SUNTORY LIMITED et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,BR,CA,CN,CZ,DE,IL,JP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AL,AM,AT,AZ,BA,BB,BY,CH,CR,CU,DK,DM,EE,ES,FI,GB,GD,GE,GH,GM,
   HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,
   SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1). .

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

Kiwa Mpay

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
ISHIDA, Takashi
A. Aoki, Ishida & Associates
Toranomon 37 Mori Building
5-1, Toranomon 3-chome
Minato-ku
Tokyo 105-8423
JAPON

受信
12.3.13

138

Date of mailing (day/month/year)	
02 March 2000 (02.03.00)	
Applicant's or agent's file reference G899-PCT	**IMPORTANT NOTICE**
International application No. PCT/JP99/04503	**International filing date** (day/month/year) 20 August 1999 (20.08.99)
Priority date (day/month/year) 21 August 1998 (21.08.98)	
Applicant SUNTORY LIMITED et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   02 March 2000 (02.03.00) under No. WO 00/10982

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 239/96, 403/12, 413/12, A61K 31/505, A61P 9/10, 11/06, 37/08

A1

(11) International Publication Number: WO 00/10982

(43) International Publication Date: 2 March 2000 (02.03.00)

(21) International Application Number: PCT/JP99/04503

(22) International Filing Date: 20 August 1999 (20.08.99)

(30) Priority Data:
10/235633 21 August 1998 (21.08.98) JP

(71) Applicant *(for all designated States except US)*: SUNTORY LIMITED [JP/JP]; 1–40, Dojimahama 2–chome, Kita–ku, Osaka–shi, Osaka 530–8203 (JP).

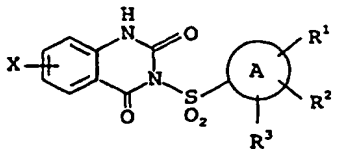
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: FUKAMI, Harukazu [JP/JP]; 36, Shimadezaike–cho, Kisshoin, Minami–ku, Kyoto 601–8373 (JP). ITO, Akiko [JP/US]; 261 Congressional Ln. #708, Rockvill, MD 20852 (US). IMAJO, Seiichi [JP/JP]; 1–4–8, Iguchido, Ikeda–shi, Osaka 563–0023 (JP).

(74) Agents: ISHIDA, Takashi et al.; A. Aoki, Ishida & Associates, Toranomon 37 Mori Building, 5–1, Toranomon 3–chome, Minato–ku, Tokyo 105–8423 (JP).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: QUINAZOLINE DERIVATIVES AND PHARMACEUTICAL APPLICATIONS THEROF



(I)

(57) Abstract

A quinazoline derivative having formula (I), or a pharmaceutically acceptable salt thereof, which has a chymase inhibitory activity and suppresses the exacerbation of vascular permeability induced by chymase and useful as a medicament, and a pharmaceutical composition containing the same as an essential ingredient.

PATENT COOPERATION TREATY

REC'D 21 SEP 2000
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
G899-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP99/04503	20/08/1999	21/08/1998
International Patent Classification (IPC) or national classification and IPC C07D239/96		
Applicant SUNTORY LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/03/2000	19.09.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Scruton-Evans, I Telephone No. +49 89 2399 8272

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP99/04503

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-41 as originally filed

Claims, No.:

11 (part), 12 (part) as originally filed

1-10,11 (part),12 (part), 13 with letter of as received on 18/08/2000 25/08/2000

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

see separate sheet

Section V

The following documents cited in the Search Report are referred to in this communication;

Canadian Journal of Cardiology, 11,supp F,13f-19f 1995 (1)
EP-A-0 795 548 (2)
J.Med.Chem, 40(14),1997, 2156-2163 (3)
JP05169832 (4)
WO-A-9745400 (5)

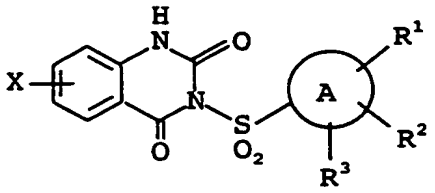
With regard to the requirement for novelty (Article 33(2) of the PCT); for the compounds of claim 1, the document (1) is a general document and (3) discloses imidazolidinones. The document (2) has a specific example (148) disclosed therein which is corresponds to claim 1 and 11 and 12 in the present application (specifically example 4 of the present application), and this example has been excluded from the claims 1,11 and 12 by means of a disclaimer. It is accepted that there is no overlap in the general formulae when R1 in the present application is alkyl substituted with CO_2H and R_2 and R3 are H if the definitions in (2) are interpreted such that the definition of a carboxyl group for R1 and R2 stands alone, and is not a possibility for the substituent on the alkyl. In (5) there is a general overlap of the formula with that of the present application claim 11 and 12, but the overlap is not novelty destroying. Document (4) discloses compounds differing from those of claims 11 and 12 in that the substituents on R1 are not those of the present application R1,R2 and R3. Article 33(2) of the PCT is thus satisfied.

With regard to the requirement for inventive step (Article 33(3) of the PCT), it is considered that the man skilled in the art, faced with the problem of providing further novel chymase inhibitors would have considered that the compounds of the present application, which differ from those of (2) only in the substitution on the ring A would have the same qualitative activity, especially as some of the substituents are already considered in the same activity field to be interchangeable (see (3), Table 1). Thus the problem underlying the present application must have been the provision of further novel compounds with unexpected advantages re the closest prior art (2), and in the absence of any evidence of such advantages, Article 33(3) of thePCT cannot be considered to have been satisfied. If the suppression of the exacerbation of vascular permeability induced by chymase is an

unexpected or additional activity, then this should be substantiated. For the intermediates, inventive step will be dependent on a positive acknowledgement for the end products.
The terms "substituted" when used in the groups R_2 and R_3 should be replaced by the exact definitions given in the description, page 7,8.
The term "lower" should be deleted from the claims, as a C-atom content has already been given.

CLAIMS

1. (Amended) A quinazoline derivative having the following formula (1) and a pharmaceutically acceptable salt thereof:



(1)

wherein the ring A represents an aryl group;

R^1 represents a hydroxyl group, an amino group, a C_1 to C_4 lower alkylamino group which may be substituted with a carboxylic acid group, a C_7 to C_{10} lower aralkylamino group which may be substituted with a carboxylic acid group, an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, a C_1 to C_4 lower alkyl group substituted with a carboxylic acid group, or a C_2 to C_4 lower alkylene group which may be substituted with a carboxylic acid group;

R^2 and R^3 may be the same or different and represent a hydrogen atom, an unsubstituted or substituted C_1 to C_4 lower alkyl group, a halogen atom, a hydroxyl group, a C_1 to C_4 lower alkoxyl group, an amino group, an unsubstituted or substituted C_1 to C_4 lower

alkylamino group, an unsubstituted or substituted C_7 to C_{10} aralkylamino group, an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, or a carboxylic acid group or

when the ring A is a benzene ring, R^1 and R^2 may form, together with the substituting benzene ring, a fused heterocyclic ring which may be substituted with a carboxylic acid and in which the carbon atom in the ring may form a carbonyl group and R^3 is the same as defined above; and

X represents a hydrogen atom, a C_1 to C_4 lower alkyl group, a C_1 to C_4 lower alkoxy group, a halogen atom, a hydroxyl group, an amino group, or a nitro group, <u>with the proviso that, when the ring A is a benzene ring, R^1 is an amino group and both R^2 and R^3 are a hydrogen atom, R^1 is not positioned at the para-position to the sulfonyl group.</u>

2. A quinazoline derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, wherein, in the formula (1), R^1 is a hydroxyl group, an amino group, a C_1 to C_4 lower alkylamino group substituted with a carboxylic acid group, or an amino group acylated with a C_1 to C_4 lower aliphatic acid substituted with a carboxylic acid group.

3. A quinazoline derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1 or 2, wherein,

in the formula (1), R^2 is a carboxylic acid group or a hydrogen atom.

4. A quinazoline derivative or a pharmaceutically

acceptable salt thereof as claimed in any one of claims 1 to 3, wherein R^3 in the formula (I) is a hydrogen atom.

5. A pharmaceutical composition comprising as an effective ingredient a pharmaceutically effective amount of a quinazoline derivative or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier therefor.

6. A chymase inhibitor having as an effective ingredient a quinazoline derivative or its pharmaceutically salt according to any one of claims 1 to 4.

7. A pharmaceutical composition as claimed in claim 5 for prevention or treatment of allergic diseases or rheumatic diseases.

8. A pharmaceutical composition as claimed in claim 5 for prevention or treatment of bronchial asthma, eczema, atopic dermatitis, mastocytosis, scleriasis, or rheumatoid arthritis.

9. A pharmaceutical composition as claimed in claim 5 for prevention or treatment of cardiac and circulatory system diseases due to the abnormal exacerbation of Angiotensin II production.

10. A pharmaceutical composition as claimed in claim 5 for prevention or treatment of cardiac insufficiency, hypercardia, stasis cardiac diseases, hypertension, arteriosclerosis, peripheral circulatory diseases, revasoconstriction after PTCA, diabetic renal disorders or non-diabetic renal disorders, coronary diseases including cardiac infarction, angioendothelia, or vascular disorders accompanying arterialization and atheroma.

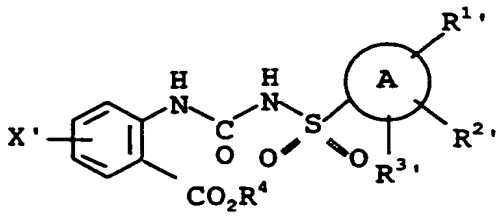
11. (Amended) A sulfonylurea derivative having the formula (4):

an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, or a carboxylic acid group or

when the ring A is a benzene ring, R^1 and R^2 may form, together with the substituting benzene ring, a fused heterocyclic ring which may be substituted with a carboxylic acid and in which the carbon atom in the ring may form a carbonyl group and R^3 is the same as defined above; and

X' is X, which may be protected with a protecting group and which represents a hydrogen atom, a C_1 to C_4 lower alkyl group, a C_1 to C_4 lower alkoxyl group, a halogen atom, a hydroxyl group, an amino group, or a nitro group, with the proviso that, when the ring A is a benzene ring, R^1 is an amino group and both R^2 and R^3 are a hydrogen atom, R^1 is not positioned at the para-position to the sulfonyl group.

12. (Amended) A sulfonylurea derivative having the formula (7):



(7)

wherein, the ring A represents an aryl group;

$R^{1'}$ is R^1, which may be protected with a protecting group and which represents a hydroxyl group,

amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, or a carboxylic acid group or

when the ring A is a benzene ring, R^1 and R^2 may form together with the substituting benzene ring a fused heterocyclic ring which may be substituted with a carboxylic acid and in which the carbon atom in the ring may form a carbonyl group and R^3 is the same as defined above;

R^4 represents a protecting group for a carboxyl group; and

X' is X, which may be protected with a protecting group and which represents a hydrogen atom, a C_1 to C_4 lower alkyl group, a C_1 to C_4 lower alkoxy group, a halogen atom, a hydroxyl group, an amino group, or a nitro group, with the proviso that, when the ring A is a benzene ring, R^1 is an amino group and both R^2 and R^3 are a hydrogen atom, R^1 is not positioned at the para-position to the sulfonyl group.

13. A method for producing a quinazoline derivative having the formula (1) according to claim 1 comprising:

allowing a sulfonylurea derivative having the formula (4) according to claim 11 to a ring-closing reaction with a condensation agent or

deprotecting a carboxyl group of the sulfonylurea derivative having the formula (7) according to claim 12, followed by effecting a ring-closing reaction with a condensation agent.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 April 2000 (18.04.00)	
International application No. PCT/JP99/04503	**Applicant's or agent's file reference** G899-PCT
International filing date (day/month/year) 20 August 1999 (20.08.99)	**Priority date** (day/month/year) 21 August 1998 (21.08.98)
Applicant FUKAMI, Harukazu et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 March 2000 (20.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

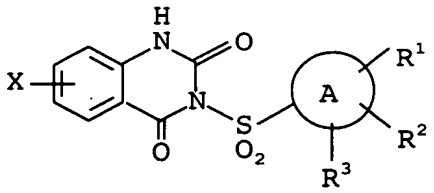
[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Kiwa Mpay
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

CLAIMS

1. A quinazoline derivative having the following formula (1) and a pharmaceutically acceptable salt thereof:



(1)

wherein the ring A represents an aryl group;

R^1 represents a hydroxyl group, an amino group, a C_1 to C_4 lower alkylamino group which may be substituted with a carboxylic acid group, a C_7 to C_{10} lower aralkylamino group which may be substituted with a carboxylic acid group, an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, a C_1 to C_4 lower alkyl group substituted with a carboxylic acid group, or a C_2 to C_4 lower alkylene group which may be substituted with a carboxylic acid group;

R^2 and R^3 may be the same or different and represent a hydrogen atom, an unsubstituted or substituted C_1 to C_4 lower alkyl group, a halogen atom, a hydroxyl group, a C_1 to C_4 lower alkoxyl group, an amino group, an unsubstituted or substituted C_1 to C_4 lower

alkylamino group, an unsubstituted or substituted C_7 to C_{10} aralkylamino group, an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, or a carboxylic acid group or

when the ring A is a benzene ring, R^1 and R^2 may form, together with the substituting benzene ring, a fused heterocyclic ring which may be substituted with a carboxylic acid and in which the carbon atom in the ring may form a carbonyl group and R^3 is the same as defined above; and

X represents a hydrogen atom, a C_1 to C_4 lower alkyl group, a C_1 to C_4 lower alkoxy group, a halogen atom, a hydroxyl group, an amino group, or a nitro group.

2. A quinazoline derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1, wherein, in the formula (1), R^1 is a hydroxyl group, an amino group, a C_1 to C_4 lower alkylamino group substituted with a carboxylic acid group, or an amino group acylated with a C_1 to C_4 lower aliphatic acid substituted with a carboxylic acid group.

3. A quinazoline derivative or a pharmaceutically acceptable salt thereof as claimed in claim 1 or 2, wherein, in the formula (1), R^2 is a carboxylic acid group or a hydrogen atom.

4. A quinazoline derivative or a pharmaceutically

acceptable salt thereof as claimed in any one of claims 1 to 3, wherein R^3 in the formula (I) is a hydrogen atom.

5. A pharmaceutical composition comprising as an effective ingredient a pharmaceutically effective amount of a quinazoline derivative or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier therefor.

6. A chymase inhibitor having as an effective ingredient a quinazoline derivative or its pharmaceutically salt according to any one of claims 1 to 4.

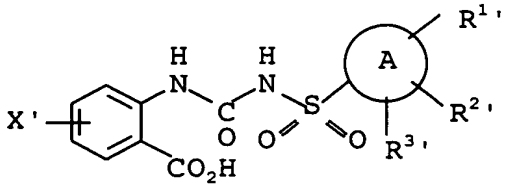
7. A pharmaceutical composition as claimed in claim 5 for prevention or treatment of allergic diseases or rheumatic diseases.

8. A pharmaceutical composition as claimed in claim 5 for prevention or treatment of bronchial asthma, eczema, atopic dermatitis, mastocytosis, scleriasis, or rheumatoid arthritis.

9. A pharmaceutical composition as claimed in claim 5 for prevention or treatment of cardiac and circulatory system diseases due to the abnormal exacerbation of Angiotensin II production.

10. A pharmaceutical composition as claimed in claim 5 for prevention or treatment of cardiac insufficiency, hypercardia, stasis cardiac diseases, hypertension, arteriosclerosis, peripheral circulatory diseases, revasoconstriction after PTCA, diabetic renal disorders or non-diabetic renal disorders, coronary diseases including cardiac infarction, angioendothelia, or vascular disorders accompanying arterialization and atheroma.

11. A sulfonylurea derivative having the formula (4):



(4)

wherein the ring A represents an aryl group;

$R^{1'}$ is R^1, which may be protected with a protecting group, and which represents a hydroxyl group, an amino group, a C_1 to C_4 lower alkylamino group which may be substituted with a carboxylic acid group, a C_7 to C_{10} lower aralkylamino group which may be substituted with a carboxylic acid group, an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, a C_1 to C_4 lower alkyl group substituted with a carboxylic acid group, or a C_2 to C_4 lower alkylene group which may be substituted with a carboxylic acid group;

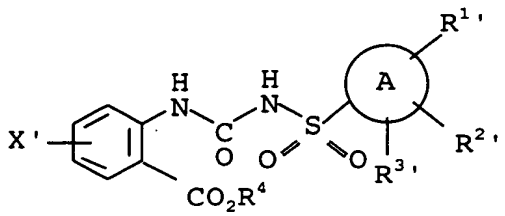
$R^{2'}$ and $R^{3'}$ are R^2 and R^3, respectively, which may be protected with a protecting group, which may be the same or different, and which represent a hydrogen atom, an unsubstituted or substituted C_1 to C_4 lower alkyl group, a halogen atom, a hydroxyl group, a C_1 to C_4 lower alkoxyl group, an amino group, an unsubstituted or substituted C_1 to C_4 lower alkylamino group, an unsubstituted or substituted C_7 to C_{10} aralkylamino group,

an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, or a carboxylic acid group or

when the ring A is a benzene ring, R^1 and R^2 may form, together with the substituting benzene ring, a fused heterocyclic ring which may be substituted with a carboxylic acid and in which the carbon atom in the ring may form a carbonyl group and R^3 is the same as defined above; and

X' is X, which may be protected with a protecting group and which represents a hydrogen atom, a C_1 to C_4 lower alkyl group, a C_1 to C_4 lower alkoxyl group, a halogen atom, a hydroxyl group, an amino group, or a nitro group.

12. A sulfonylurea derivative having the formula (7):



(7)

wherein, the ring A represents an aryl group;

$R^{1'}$ is R^1, which may be protected with a protecting group and which represents a hydroxyl group,

an amino group, a C_1 to C_4 lower alkylamino group which may be substituted with a carboxylic acid group, a C_7 to C_{10} lower aralkylamino group which may be substituted with a carboxylic acid group, an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, a C_1 to C_4 lower alkyl group substituted with a carboxylic acid group, or a C_2 to C_4 lower alkylene group which may be substituted with a carboxylic acid group;

$R^{2'}$ and $R^{3'}$ are R^2 and R^3, respectively, which may be protected with a protecting group, which may be the same or different and which represent a hydrogen atom, an unsubstituted or substituted C_1 to C_4 lower alkyl group, a halogen atom, a hydroxyl group, a C_1 to C_4 lower alkoxyl group, an amino group, an unsubstituted or substituted C_1 to C_4 lower alkylamino group, an unsubstituted or substituted C_7 to C_{10} lower aralkylamino group, an amino group acylated with a C_1 to C_4 lower aliphatic acid which may be substituted with a carboxylic acid group, an amino group acylated with an aromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group acylated with a heteroaromatic ring carboxylic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a C_1 to C_4 lower alkanesulfonic acid which may be substituted with a carboxylic acid group, an

amino group sulfonylated with an aromatic ring sulfonic acid which may be substituted with a carboxylic acid group, an amino group sulfonylated with a heteroaromatic ring sulfonic acid which may be substituted with a carboxylic acid group, or a carboxylic acid group or

when the ring A is a benzene ring, R^1 and R^2 may form together with the substituting benzene ring a fused heterocyclic ring which may be substituted with a carboxylic acid and in which the carbon atom in the ring may form a carbonyl group and R^3 is the same as defined above;

R^4 represents a protecting group for a carboxyl group; and

X' is X, which may be protected with a protecting group and which represents a hydrogen atom, a C_1 to C_4 lower alkyl group, a C_1 to C_4 lower alkoxy group, a halogen atom, a hydroxyl group, an amino group, or a nitro group.

13. A method for producing a quinazoline derivative having the formula (1) according to claim 1 comprising:

allowing a sulfonylurea derivative having the formula (4) according to claim 11 to a ring-closing reaction with a condensation agent or

deprotecting a carboxyl group of the sulfonylurea derivative having the formula (7) according to claim 12, followed by effecting a ring-closing reaction with a condensation agent.

PCT REQUEST

G899-PCT

Original (for **SUBMISSION**) - printed on 30.09.1999 04:24:14 PM

0 0-1	**For receiving Office use only** International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4 0-4-1	**Form - PCT/RO/101 PCT Request** Prepared using	PCT-EASY Version 2.82 (updated 01.01.1999)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	Japanese Patent Office (RO/JP)
0-7	**Applicant's or agent's file reference**	G899-PCT
I	**Title of invention**	QUINAZOLINE DERIVATIVES AND APPLICATIONS THEREOF
II II-1 II-2 II-4 II-5 II-6 II-7	**Applicant** This person is: Applicant for Name Address: State of nationality State of residence	 applicant only all designated States except US SUNTORY LIMITED 1-40, Dojimahama 2-chome, Kita-ku, Osaka-shi, Osaka 530-8203 Japan JP JP
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	**Applicant and/or Inventor** This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor US only FUKAMI, Harukazu 36, Shimadezaike-cho, Kisshoin, Minami-ku, Kyoto 601-8373 Japan JP JP

PCT REQUEST G899-PCT

Original (for **SUBMISSION**) - printed on 20.08.1999 04:27:15 PM

III-2	**Applicant and/or Inventor**	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	ITO, Akiko
III-2-5	Address:	261 Congressional Ln. #708, Rockvill, MD 20852 United States of America
III-2-6	State of nationality	JP
III-2-7	State of residence	US
III-3	**Applicant and/or Inventor**	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	IMAJO, Seiichi
III-3-5	Address:	1-4-8, Iguchido, Ikeda-shi, Osaka 563-0023 Japan
III-3-6	State of nationality	JP
III-3-7	State of residence	JP
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	ISHIDA, Takashi
IV-1-2	Address:	A. AOKI, ISHIDA & ASSOCIATES Toranomon 37 Mori Bldg., 5-1, Toranomon 3-chome, Minato-ku, Tokyo 105-8423 Japan
IV-1-3	Telephone No.	03-5470-1900
IV-1-4	Facsimile No.	03-5470-1911
IV-2	**Additional agent(s)**	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	NISHIYAMA, Masaya

PCT REQUEST

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Original (for SUBMISSION) - printed on 20.08.1999 04:27:15 PM

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AL AM AT AU AZ BA BB BG BR BY CA CH&LI CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
V-3	National Patent (States which have become party to the PCT after the issuance of this version of EASY)	AE United Arab Emirates ZA South Africa CR Costa Rica DM Dominica
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	**Exclusion(s) from precautionary designations**	NONE
VI-1	**Priority claim of earlier national application**	
VI-1-1	Filing date	21 August 1998 (21.08.1998)
VI-1-2	Number	Patent Application 10-235633
VI-1-3	Country	JP
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

PCT REQUEST G899-PCT

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VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description	41	-
VIII-3	Claims	7	-
VIII-4	Abstract	1	g899-abstract.txt
VIII-5	Drawings	0	-
VIII-7	TOTAL	53	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-17	Other (specified):	patent revenue stamps	-
VIII-18	**Figure of the drawings which should accompany the abstract**		
VIII-19	**Language of filing of the international application**	English	
IX-1	**Signature of applicant or agent**		
IX-1-1	Name (LAST, First)	ISHIDA, Takashi	Takashi Ishida
IX-2	**Signature of applicant or agent**		
IX-2-1	Name (LAST, First)	NISHIYAMA, Masaya	M. Nishiyama

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10-1	**Date of actual receipt of the purported International application**	
10-2	**Drawings:**	
10-2-1	Received	
10-2-2	Not received	
10-3	**Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application**	
10-4	**Date of timely receipt of the required corrections under PCT Article 11(2)**	
10-5	**International Searching Authority**	ISA/EP
10-6	**Transmittal of search copy delayed until search fee is paid**	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	**Date of receipt of the record copy by the International Bureau**	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ISHIDA,TAKASHI
A. AOKI, ISHIDA, & ASSOCIATES
Toranomon 37 Mori Bldg., 5-1,
Toranomon 3-chome, Minato-Ku
TOKYO 105-8423
JAPON

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受信
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.09.00
Applicant's or agent's file reference G899-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP99/04503	20/08/1999	21/08/1998

Applicant
SUNTORY LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel.+49 89 2399-8012

Form PCT/IPEA/416 (July 1992)